Compartmentalized Signaling in Neurons – from Cell Biology to Neuroscience

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Summary

Neurons are the largest known cells, with complex and highly polarized morphologies. As such, neuronal signaling is highly compartmentalized, requiring sophisticated transfer mechanisms to convey and integrate information within and between sub-neuronal compartments. Here we survey different modes of compartmentalized signaling in neurons, highlighting examples wherein the fundamental cell biological processes of protein synthesis and degradation, membrane trafficking, and organelle transport are employed to enable the encoding and integration of information, locally and globally within a neuron. Comparisons to other cell types indicate that neurons accentuate widely shared mechanisms, providing invaluable models for the compartmentalization and transfer mechanisms required and used by most eukaryotic cells.

Keywords

Neurotrophin, importin, receptor tyrosine kinase, axonal transport, local translation, mRNA localization.

'In Brief'

Terenzio et al. survey the influence of neuronal size and polarization on compartmentalized signaling, highlighting roles for protein synthesis and degradation, membrane trafficking and organelle transport. Neuronal mechanisms provide invaluable models for studying the cell biology of signaling in diverse cell types.

Introduction

Neurons are one of the most diverse class of cells known in nature. They are characterized by specialized polarized morphologies and are clearly compartmentalized into pre- and post-synaptic regions, synapse, dendrite, soma, and axon, which are essential for their functions. Neurons are also the largest known cells, with typical process lengths ranging from millimeters to centimeters in many species, and axons that can reach meters in large mammals. This combination of specialized morphology with extreme length imposes a need for signals to be actively transferred between neuronal compartments, since intracellular signal propagation by passive diffusion has a range limited to tens of micrometers at most (Kholodenko, 2003; Wiegert et al., 2007). Signaling within and between neuronal compartments requires the deployment of sophisticated mechanisms to set the basal conditions that allow such information processing and to ensure transmission of the encoded data to its final destination. Their extreme specializations, size, polarization and excitability has generally restricted biologists from considering neurons as models for anything except themselves. However, as we discuss below, neurons largely accentuate mechanisms that are employed to varying degrees by all cell types, and as such provide invaluable "lead models" for cell biology.

Initial attempts to analyze compartmentalized signaling in neurons were aimed at generating conditions that would allow the targeted interrogation of different compartments. Radioactive labelling was extensively used early on to track ligand movements from axon terminals to somata *in vivo* (Oppenheim, 1996). Although sensitive and easy to quantify, the limited spatial and temporal resolution of radiolabeling, together with the inability to follow multiple radioactive probes simultaneously, spurred efforts to develop better tools. Initially these tools included the direct fluorescent labeling of ligands or receptors, or the labeling of antibodies and other biological reagents to track the different components of signaling systems (Bronfman et al., 2003; Lessmann and Brigadski, 2009; Watson et al., 1999). Recent developments in this area include quantum dot probes that are detectable by both fluorescence and electron microscopy at up to single-molecule resolution (Cui et al., 2007; Gluska et al., 2016), and probes conjugated to colloidal gold or super-paramagnetic nanoparticles (Steketee et al., 2011). In addition to probes based on endogenous signaling components, neurotrophic viruses and bacterial toxins

that target specific transport and compartmentalization mechanisms have also been exploited to develop novel tools to probe neuronal signaling and transport (Bercsenyi et al., 2013; Salinas et al., 2010). Caged and "click" chemistries and subcellular optogenetic tools are the latest waves in reagent development in this line, offering expanding possibilities for the spatiotemporal manipulation of signaling systems at increasing resolutions (Agetsuma et al., 2017; Kolar and Weber, 2017).

Spatially restricted activation of neuronal signaling was initially carried out in a compartmentalized device, called a Campenot chamber, that consists of compartments separated by teflon dividers sealed onto a tissue culture dish (Campenot, 1977). The sealant underlying the teflon dividers allows for neurite penetration while maintaining fluidic isolation between compartments, hence these devices were employed by a number of groups to analyze neurotrophic factor signaling (Campenot and MacInnis, 2004). Another widely used device is an adaptation of the Boyden chamber, consisting of two compartments separated by a microporous membrane with pore sizes that allow the passage of only axons or dendrites (Willis and Twiss, 2011). While technically less challenging to set up than the Campenot chamber, these filters do not easily lend themselves to fluidic isolation of the compartments, and have been used primarily as a means of harvesting different subcellular compartments for biochemical analyses. More recently a new generation of devices have been described that utilize microfluidics to separate signaling compartments (Taylor and Jeon, 2011). These microfluidics chambers are transparent and can be used in combination with glass-bottomed tissue culture dishes, hence are compatible with diverse live-imaging techniques (Zhang et al., 2015). Their inherent design flexibility makes them particularly suitable to shape different gradients of signaling molecules, isolate different regions of a neuron, or assemble topologically complex arrays of neurons, glia and supporting cells (Park et al., 2009; Zahavi et al., 2015). These unique features establish microfluidic chambers as the current tool of choice in many studies of signaling compartmentalization in neurons.

The tools and approaches briefly summarized above have been employed in many studies of neuronal signaling. Given diffusion limitations, long distance signaling between neuronal compartments requires rapid transport mechanisms utilizing either calcium waves (Cho et al.,

2013; Gelens et al., 2014; Yamada et al., 2008) or motor-driven mechanisms (Rishal and Fainzilber, 2014; Saito and Cavalli, 2016). Conversely, the restriction of signaling within a single compartment requires that the full complement of effector and response machinery be recruited to a single subcellular region (Shigeoka et al., 2013). Since the full diversity of these mechanisms cannot be covered in a single review, we will focus on selected paradigms that illuminate the impact of specific cell biology mechanisms on neuronal signaling, including endosome trafficking in neurotrophic factor signaling, RNA transport and localized translation in axonal retrograde signaling, and modes of locally restricted signaling in growth cones. For other paradigms of neuronal compartmentalized signaling, we refer readers to the following recent reviews (Bading, 2013; Panayotis et al., 2015; Zahavi et al., 2017).

Neurotrophin signaling – Trk the endosome

Neurotrophin signaling via receptor tyrosine kinases (RTK) of the Trk family represents one of the best studied examples of compartmentalized signaling in the nervous system, since it has both local and long-range outcomes. Neurotrophin signals can modulate local events in axons (Willis et al., 2005) or synapses (Mitre et al., 2017), while their long-range effects require transport from axon tips to the soma (Yamashita and Kuruvilla, 2016). Mobley and colleagues suggested that such long-range signaling could be mediated by signaling endosomes formed by the internalization of ligand-bound Trks from the plasma membrane (Grimes et al., 1996). This hypothesis has been supported by several studies showing that activated Trk receptors and their downstream signaling components are present in endosomes (Grimes et al., 1997; Riccio et al., 1997; Watson et al., 1999) (Figure 1). Follow-up studies established crucial roles for signaling endosomes in growth factor signaling in neurons, while noting diverse characteristics of these organelles in different types, or stages of maturation, of neurons (Barford et al., 2017; Harrington and Ginty, 2013; Schmieg et al., 2013).

TrkA is the canonical receptor for nerve growth factor (NGF), the first characterized member of the neurotrophin family. NGF binding causes TrkA dimerization and autophosphorylation, initiating canonical RTK signaling cascades through the PI3K/AKT, Ras/ERK and PLCγ pathways (Barford et al., 2017). Different signaling adaptors may influence internalization by a variety of

endocytic pathways, including clathrin-dependent endocytosis, caveolin-mediated internalization, clathrin and caveolin-independent uptake and macroendocytosis (Barford et al., 2017; Schmieg et al., 2013). Thus, the clathrin-mediated internalization of TrkA has been associated with ERK1/2 activation in specific cell types (Howe et al., 2001; Zheng et al., 2008), while its macroendocytosis connects to ERK5 (Valdez et al., 2005). The latter process is controlled by the endocytic chaperone Pincher (Shao et al., 2002; Valdez et al., 2005). The outcome of TrkA signaling depends on its internalization state and on its intracellular trafficking (Heerssen et al., 2004; Sharma et al., 2010; Zhang et al., 2000).

Several trafficking routes have been reported for TrkA, including its constitutive endocytosis and recycling in the absence of a ligand, its anterograde endosomal transport from soma to axons upon ligand binding (Ascano et al., 2009), and its NGF-stimulated retrograde axonal transport, mediated by signaling endosomes (Howe et al., 2001; Ye et al., 2003). The uptake of TrkA, together with its ligand, and their subsequent retrograde transport in signaling endosomes along the axon is the best characterized trafficking event of the receptor (Yamashita and Kuruvilla, 2016). Additionally, TrkA-positive signaling endosomes have been described to be recycled and re-internalized upon arrival at the cell body, which might allow the receptor to escape lysosomal degradation, thereby modulating signaling output (Suo et al., 2014).

The nature of the signaling-competent endosomal compartment for Trks has defied simple categorization. In the sciatic nerve, TrkA was found to be present in a variety of endosomes, ranging from 50 to 220 nm in diameter, including multivesicular bodies (MVBs) and several coated and uncoated organelles (Bhattacharyya et al., 2002). Heterogeneity in TrkA retrograde signaling endosomes was further implied by studies describing their association and axonal co-transport with both Rab5 and Rab7, which are traditionally believed to be markers of early and late endosomes, respectively (Philippidou et al., 2011; Saxena et al., 2005; Zhang et al., 2015; Zhang et al., 2013). This apparent heterogeneity might be due to a transition between different stages, since a switch from Rab5 to Rab7 has been reported during endosomal maturation (Rink et al., 2005), or due to coexistence of both Rab7- and Rab 5-positive populations with different

functions, possibly indicating a requirement for balance between Rab5/Rab7 arms of the signaling endosome system (Liu et al., 2017).

In PC12 cells, TrkA-positive endosomes were described to recruit RabGAP5, which inactivates Rab5, delaying the organelle's maturation and prolonging signaling and neurite outgrowth (Bucci et al., 2014; Liu et al., 2007). Expression of a dominant-negative Rab7 in PC12 cells enhances NGF-mediated signaling (Saxena et al., 2005), while it abolishes axonal retrograde transport of TrkB-positive endosomes in motor neurons (Deinhardt et al., 2006). Additional studies have implicated late endosomes and MVBs in the transport of neurotrophins and their receptors (Sandow et al., 2000; Terenzio et al., 2014; Valdez et al., 2005). Interestingly, a very recent study described TrkB-signaling endosomes to be Rab7-positive, late-stage autophagosomes that undergo retrograde transport through their association with the known clathrin adaptor, AP-2 (Kononenko et al., 2017). Indeed, Trk signaling was shown to be modulated by autophagy in both neurons (Smith et al., 2014) and cycling cells (Mazouffre et al., 2017). These findings support early proposals that autophagy might serve to initiate retrograde signaling in axons (Kaasinen et al., 2008). Interestingly, recent findings support the compartmentalized regulation of autophagy in neurons (Maday and Holzbaur, 2016), although the link between these observations and Trk signaling remains an open question. Thus, although it is clear that trafficking properties and the state of endosomal maturation affect Trk signaling, a diverse spectrum of organelles have been implicated in Trk signaling. Studies that exploit pathological mutations of Rab7 might be key to furthering our understanding of these aspects of neurotrophin trafficking and signaling, as discussed below.

Once TrkA signaling endosomes reach the soma, they can continue to signal for long periods of time, indeed, in one report, a pool of the receptor was found to escape degradation for up to 25 hours in cultured neurons (Suo et al., 2014). The transit time of the complex in long mammalian nerves may necessitate even longer maintenance of the signal. Such persistent signaling is facilitated by local somatic recycling of the receptor, mediated by TrkA sorting to Rab11-positive recycling endosomes that escape lysosomal targeting and degradation (Fig 1) (Suo et al., 2014). In addition, somatic TrkA undergoes constitutive endocytosis and recycling, generating an endosomal receptor pool without NGF stimulation (Ascano et al., 2009).

Interestingly, a very recent study suggested the existence of a quality control mechanism that ensures the axonal targeting specifically of somatic inactive TrkA receptors. This mechanism involves active dephosphorylation of TrKA via the ER-resident protein tyrosine phosphatase, PTP1B (Yamashita et al., 2017).

Rab11-positive endosomes can traffic TrkA outwards to the axon (Ascano et al., 2009), and a similar Rab11-dependent endosomal recycling has been described for TrkB in hippocampal dendrites (Lazo et al., 2013). The sorting receptor sortilin has been described to associate with Trks to enhance their anterograde transport (Vaegter et al., 2011), and perturbation of the recycling or anterograde transport of Trks disrupts their subsequent signaling (Arimura et al., 2009; Ascano et al., 2009; Huang et al., 2011). Finally, axon-derived TrkA signaling endosomes were recently described to regulate synaptic maintenance by being translocated into dendrites after their arrival in sympathetic neuron somata (Lehigh et al., 2017). Thus, endosomal trafficking is involved in the replenishment of Trk in axons and in the amplification or modulation of signaling in the soma, as well as in canonical retrograde signaling from axon tips to somata (Figure 1).

The concept of endosomes as signaling platforms was hypothesized for neurotrophin signaling in neurons due to the long distances that exist between where ligand and receptor interact at the axon tip, to the soma, where transcriptional or survival responses take place. The possibility that RTK internalization also occurs as a signaling step in dividing cells was not immediately obvious, and for many years it was assumed in the field that internalized RTKs in non-neuronal cells traverse the endocytic pathway to their degradation as a way to shut down their signaling (Villasenor et al., 2016). However, over the past few years, a series of studies have delineated signaling roles for RTK-containing endosomes in cycling cells. The evidence for this role includes the colocalization of signaling adaptors with phosphorylated EGFR on endosomes (Fortian and Sorkin, 2014; Villasenor et al., 2015). Quantitative analyses have also shown continued signaling of EGFRs from endosomes, and decoupling of the dephosphorylation and degradation steps, demonstrating the modulation of EGFR signaling within the endosomal system (Baumdick et al., 2015; Villasenor et al., 2015). Thus, the signaling endosome is not unique to neurons, but rather represents a general mechanism that has gained prominence in neurons due to their

morphological and functional requirements. Neurons might therefore provide a cellular model in which to study aspects of compartmentalized signaling of Trks and other RTKs that cannot easily be addressed in cycling cells. A mechanistic understanding of Trk compartmentalized signaling may therefore have broad translational implications, given recent findings that reinforce the roles of this receptor family as drivers of tumorigenesis (Hayakawa et al., 2017; Lawn et al., 2015).

An endosome-free route for locally translated signals

In addition to the above, diverse studies have highlighted non-vesicular, motor-dependent mechanisms for the long-distance transfer of signals between neuronal compartments (Figure 2). Most of these studies have focused on retrograde signal transfer along axons or dendrites, highlighting roles for mRNA localization and localized protein synthesis in generating key components of transported signaling complexes. Early studies of injured axons in Aplysia suggested that certain proteins can utilize nuclear localization signals (NLS) for their retrograde transport from lesion site to soma (Schmied and Ambron, 1997; Schmied et al., 1993). Studies in the mammalian peripheral nerve then found components of the nuclear import machinery to be in association with axonal dynein (Hanz et al., 2003). Moreover, formation of this importins-dynein complex was shown to require the local translation of importin β1 in injured sensory axons (Hanz et al., 2003; Perry et al., 2012). Additional components of the complex were also found to be locally translated, including the regulator RanBP1 (Yudin et al., 2008) and signaling molecules, such as the transcription factor STAT3 (Ben-Yaakov et al., 2012). Importins and their transcription factor cargos have also been implicated in other paradigms of long-distance signaling, including synapse to nucleus signaling (Ch'ng et al., 2012; Jeffrey et al., 2009; Thompson et al., 2004; Uchida and Shumyatsky, 2017; Uchida et al., 2017), and survival-regulating signaling during development (Ji and Jaffrey, 2014) or neurodegeneration (Baleriola et al., 2014).

Local translation has also been suggested to regulate the association of different signaling complexes with the dynein retrograde motor, via localized synthesis of different dynein

cofactors (Villarin et al., 2016). In addition, a diverse range of scaffolding proteins link different signals to retrograde transport complexes, including dual leucine zipper kinase (DLK)(Shin et al., 2012), JNK interacting protein 3 (JIP3) (Abe et al., 2009), and vimentin (Perlson et al., 2005).

Vimentin provides a compelling example of how local translation and post-translational mechanisms combine to enable the protected long-distance transport of a signaling molecule without a need for endosomes. A proteomic screen in Lymnaea neurons provided the first evidence that linked type III intermediate filaments (IF) to retrograde axonal signaling (Perlson et al., 2004). Vimentin was then identified as being the principal retrogradely transported mammalian IF in the sciatic nerve; it was present in the axoplasm as soluble fragments, which were generated by local translation and by calpain-mediated cleavage (Perlson et al., 2005). The de novo translated and cleaved vimentin binds phosphorylated Erks (pErk), linking pErk to dynein via direct binding of vimentin to importin β1. Vimentin binding to pErk shields the phosphorylation sites on the kinase, protecting them from phosphatases (Perlson et al., 2006). A very similar mechanism was recently described for NMDA receptor signaling from synapse to nucleus, wherein proteolytic cleavage fragments of the IF α-internexin associate with Erk and its phosphorylated substrate Jacob, protecting Jacob from dephosphorylation en route (Karpova et al., 2013). Proteolytic cleavage also features in the generation of soluble fragments from transmembrane receptors for axonal signaling (Bronfman, 2007; Perlson et al., 2009). Thus, local translation and proteolysis generate non-endosomal complexes that enable phosphorylated signals to be transported over long distances in injured nerve, protecting them from dephosphorylation by steric hindrance brought about by protein-protein interactions.

Local translation enables localized cytoskeletal regulation

The mechanisms discussed above enable signaling between neuronal compartments, wherein signals are generated in one compartment and transduced to elicit effects in a distinct and often distant compartment. Neuronal compartmentalization and diffusion limits also help to restrict signaling to an individual compartment, in some cases to a focal region that spans only a few micrometers from the signal origin. In this section, we focus on compartmentalized

signaling via cytoskeletal regulation of growth cone navigation and axonal branching, and on the role of local translation in these processes (Batista and Hengst, 2016; Shigeoka et al., 2013). For a comprehensive description of compartmentalized signaling and local translation in synapses and dendrites, we refer readers to the following recent reviews (Donlin-Asp et al., 2017; Rangaraju et al., 2017; Schieweck et al., 2016).

Early studies of growth cones demonstrated their responsiveness to guidance cues even when cell bodies were physically detached from the growing axon, and also demonstrated that both calcium signaling and local protein synthesis were involved in this response (Campbell and Holt, 2001; Ming et al., 2002). The local translation response was found to depend on the nature and concentration of the guidance cue (Manns et al., 2012; Nedelec et al., 2012), as well as its precise localization (Brittis et al., 2002; Leung et al., 2006). One prominent locally translated protein that functions in growth cone guidance turned out to be beta-actin, the mRNA of which localizes to growth cones together with its main RBP, Zipcode-Binding Protein 1 (ZBP1) (Yao et al., 2006). The inhibition of local beta-actin synthesis or of the binding of its mRNA to ZBP1 perturbs calcium-mediated growth cone guidance (Welshhans and Bassell, 2011; Yao et al., 2006). Translation can be locally regulated in the growth cone by multiple processes, including phosphorylation of the RBP to release the cargo mRNA (Sasaki et al., 2010), microRNA-mediated gating of mRNA selection (Bellon et al., 2017), and even direct contact between a guidance receptor and the translation machinery (Tcherkezian et al., 2010). By contrast, ubiquitination is reportedly upregulated in the growth cone, establishing a balance between the local synthesis and local degradation of key proteins (Figure 3) (Deglincerti et al., 2015). Finally, a very recent study has reported that arginylation in the growth cone is mediated by the co-transport of beta-actin and the arginyltransferase, ATE1; their concomitant local translation is followed by the subsequent arginylation of the de novo synthesized beta actin (Wang et al., 2017). This example presents an intriguing situation in which an enzyme and its substrate(s) are both synthesized locally, ensuring tight spatiotemporal restriction of the modification.

In addition to growth cones, axonal branch points provide localized foci for compartmentalized signaling that are highly dependent on local translation. NGF has been shown to promote sensory axon branching through the regulation of the actin cytoskeleton by canonical signaling

mechanisms coupled with localized protein synthesis (Spillane et al., 2012). Focal neurotrophin stimuli recruited diverse mRNAs to the point of stimulus in the axon, which was also the location for their translation (Willis et al., 2007). Partly shared RBPs target the mRNAs involved to axons (Donnelly et al., 2011; Yoo et al., 2013). However, competition experiments have shown that different mRNAs support different outcomes, for example, the local translation of β-actin supported axon branching, while the local translation of GAP-43 mRNA facilitated elongating growth (Donnelly et al., 2013). Translational machinery and RNA granules are targeted to branching sites in axons, with the subsequent recruitment of mitochondria promoting actin-dependent branching by providing the energy for localized translation (Spillane et al., 2013; Wong et al., 2017). Thus, the local control of growth cone guidance and of axon branching are achieved through a balance of localized synthesis, degradation, and through the modification of key proteins, thereby transducing focal signals into localized cytoskeletal changes (Figure 3).

mRNA localization and subcellular protein synthesis play prominent roles in the compartmentalization of signaling in neurons, as outlined above. However, this is not restricted to neurons, and it is becoming increasingly apparent that the subcellular regulation of mRNA translation is a widespread phenomenon. RNA transport and local protein synthesis has been reported in the elongated processes of Schwann cells (Gould and Mattingly, 1990) and of oligodendrocytes (Laursen et al., 2011), implicating the local translation of myelin basic protein in CNS myelination (Torvund-Jensen et al., 2014). More recent studies have reported that the local translation of specific mRNA subsets occurs in the processes and terminal ‘endfeet’ of both astrocytes (Boulay et al., 2017; Sakers et al., 2017) and radial glia progenitors (Pilaz et al., 2016). Outside of the nervous system, local translation has been described to occur in the cellular extremities of diverse cell types, including fibroblasts (Buxbaum et al., 2015; Condeelis and Singer, 2005; Perry et al., 2016), mesenchymal-like cells (Mardakheh et al., 2015), and intestinal epithelia (Moor et al., 2017). The suggested functional roles of localized translation in peripheral subcellular compartments range from communication with adjacent cells (Sakers et al., 2017) to regulation of the size or growth of the originating cell (Perry et al., 2016). Given the relative ease with which localized translation can be analyzed and isolated in neuronal sub-

compartments, as compared to most cycling cell types, studies of mRNA transport and local translation in neurons will likely provide broadly applicable insights in the coming years.

Location, location and location – how cell biology sets the stage for compartmentalized signaling

The mechanisms outlined above highlight the fact that compartmentalized signaling in neurons largely depends on cell biological mechanisms that ensure that the required molecules are available or generated in the right place at the right time. A comprehensive understanding of compartmentalized signaling therefore requires us to fully grasp its underlying cell biology, and there are many lacunae in our understanding of these mechanisms, especially in neurons. For example, the main molecular motors required for active transport of the signaling complexes described above are dynein or kinesin microtubule-associated motors. There are multiple members of each of these motor families, which function in complexes with a plethora of adaptor proteins (Hirokawa and Tanaka, 2015; Schiavo et al., 2013). The nature of the transported signals is determined by the composition of the motor complex and its associated adaptors, which control to a large extent the specific response to a given stimulus (Hoogenraad and Akhmanova, 2016; Schiavo et al., 2013). The precise roles of many motor complex components and adaptor proteins are still unknown, and a detailed characterization of their subcellular expression, cargo specificities and regulation in neurons is required for progress to be made in the field. Similarly, numerous membrane trafficking factors regulate the fate of endosomal cargos, most prominently the small GTPase families, comprising the Rabs, Arls and Rals (Farias et al., 2017; Wandinger-Ness and Zerial, 2014). Rabs facilitate vesicle fusion, and the transport and maturation of vesicles, by recruiting a cohort of effectors to membranes and, as noted above, a few individual Rabs act as markers of specific endosomal compartments (Pfeffer, 2017). Most of our knowledge about Rabs comes from studies performed on fibroblasts; however, there are 50 Rabs encoded in mammalian genomes, many of which are completely uncharacterized at the functional level. A systematic survey has revealed that approximately half of all Drosophila Rabs function specifically or predominantly in recycling endosomes in distinct subsets of neurons (Chan et al., 2011). It is therefore likely that the

characterization of Rab family dynamics in mammalian systems will shed new light on neuronal specializations in endosome-dependent signaling (Schmieg et al., 2013).

On the local translation front, the mechanisms that determine the transport of mRNA to axons and dendrites and their translational regulation are of key interest. Literally thousands of mRNAs have been identified to be present in dendritic or axonal compartments by comprehensive sequencing approaches (Cajigas et al., 2012; Minis et al., 2014; Rangaraju et al., 2017), raising the question as to how specific subgroups of these mRNAs are selected for translation in response to a cell's need. RNAs are transported in granules associated with different RBPs (Thomas et al., 2011), and the composition and diversity of such granules in axons or dendrites is largely unknown. Comparison of two preparations of distinct RNA granules revealed that they were much more heterogenous than previously anticipated, sharing only a third of their protein interactome (Fritzsche et al., 2013). The signals that sort individual mRNAs to such granules are also diverse, including UTR motifs (Andreassi and Riccio, 2009), retained introns (Sharangdhar et al., 2017), and even the post-transport remodeling of UTR's (Andreassi et al., 2017). The source and regulation of axonal ribosomes has also been contentious (Rangaraju et al., 2017; Twiss and Fainzilber, 2009). Moreover, mRNAs that encode numerous ribosomal proteins have also been found in axons and dendrites, and this is puzzling given the obligatory nucleolar steps in ribosomal biogenesis (Rangaraju et al., 2017). Two recent studies reported that functional diversity and heterogeneity exist among mammalian ribosomes (Simsek et al., 2017) and noted that heterogeneous ribosomes preferentially translate distinct mRNA ensembles (Shi et al., 2017). Thus, two major areas for research to focus on in the near future are the co-transport and regulation of different RNA ensembles in neurons, and the generation and specification of the translational machineries in neuronal processes.

Another area for future investigation will be the cross-talk that occurs between different mechanisms. For example, calcium waves and motor-driven transport are usually considered to represent two distinct signaling modes, but there are likely multiple possibilities for their integration or co-regulation. The time differential that exists between the arrival of a calcium wave versus the arrival of a motor-driven signal in the soma could also act as a potential readout of the distance of the originating stimulus (Kam et al., 2009). Conversely, the calcium-

mediated regulation of local translation in an axon (Yudin et al., 2008) or of the association of different components of a retrograde complex en route (Perlson et al., 2006), might affect the composition of the complex that eventually arrives in the soma, determining the nature of the response. Endosome-driven transport can affect RNA localization and local translation and vice versa (Cosker et al., 2016; Tasdemir-Yilmaz and Segal, 2016). Finally, the energy dependence of the mechanisms outlined above provides another potential regulatory interaction that should also be explored. Both mitochondria (Chada and Hollenbeck, 2004; Spillane et al., 2013) and glycolysis (Hinckelmann et al., 2016; Zala et al., 2013) have been linked to retrograde signaling and local translation, raising questions as to how mitochondrial and glycolytic enzyme transport are coordinated with the needs of these compartmentalized signaling mechanisms.

Pathological consequences of deficits in compartmentalized signaling

The central roles that compartmentalized signaling fulfil in neuronal physiology are also reflected by the deleterious consequences of perturbations to these mechanisms. A comprehensive coverage of all known such cases is beyond the scope of any single review, although two recent overviews provide a starting point, which we refer readers to (Brady and Morfini, 2017; De Vos and Hafezparast, 2017). Here, we summarize selected examples of genes mutated in human disease that have well-defined roles in compartmentalized signaling in neurons.

As summarized above, Rab7 has a prominent role in regulating the endosomal pathway in neurotrophin signaling. Rab7 mutations are the causative factor of a hereditary neuropathy known as Charcot-Marie-Tooth disease type 2B (CMT2B), which is characterized by muscle distal atrophy, sensory loss and axonal degeneration (Gentil and Cooper, 2012; Liu and Wu, 2017). Four CMT2B-associated Rab7 mutants have been shown to dysregulate axonal transport and to reduce retrograde signaling of NGF via TrkA in sensory neurons, followed by axonal degeneration (Zhang et al., 2013). Both Drosophila and zebrafish models of Rab7 disease-linked mutations have revealed altered axonal transport (Janssens et al., 2014; Ponomareva et al., 2016). Taken together, the findings to date implicate perturbed retrograde NGF signaling as one of the most likely explanations for the neurodegeneration that is induced by Rab7 mutations in CMT2B (Liu and Wu, 2017).

Perturbation of neurotrophin retrograde signaling has also been implicated in Huntington's disease, which is caused by polyglutamine expansions in huntingtin (Htt), a transport facilitating dynein interactor (Caviston et al., 2011). Htt and associated proteins control axonal transport of the neurotrophin, BDNF (Gauthier et al., 2004), modulating both BDNF's processivity (Weiss and Littleton, 2016) and directionality (Colin et al., 2008) of transport. The expression of mutant Htt inhibits BDNF axonal transport in striatal neurons, leading to a loss of BDNF support and to subsequent neuronal death (Gauthier et al., 2004). A model that recreated the corticostriatal circuit in microfluidic chambers was recently used to show that enhanced BDNF delivery can improve the health of mutant Htt-expressing striatal neurons (Zhao et al., 2016).

Another example of a gene family mutated in human disease is the aminoacyl-tRNA synthetases, which are ubiquitously expressed enzymes that attach amino acids to their cognate tRNA molecules in the cytoplasm and mitochondria. A number of human disease-linked tRNA synthetase mutations manifest primarily in neurodegeneration, raising the question as to which specific aspects of neuronal function are especially sensitive to these ubiquitously expressed mutants (Antonellis and Green, 2008). The prominent roles of local translation in compartmentalized signaling and in other aspects of neuronal physiology have raised the possibility that these functions might be those that are most sensitive to deficits in tRNA synthetase activity. However, a detailed analysis of CMT2D, a peripheral neuropathy caused by glycyl-tRNA synthetase (GARS) mutations, has shown that over-expression of wild-type GARS does not improve the neuropathy phenotype in heterozygous Gars mutant mice (Motley et al., 2011). Increased dosage of the disease-causing alleles caused a more severe neurological phenotype, and although the Gars missense mutations might cause some loss of function, the dominant neuropathy phenotype appears to be caused by a dose-dependent gain of function (Motley et al., 2011). Additional analyses of other tRNA synthetase disease-causing mutants in Drosophila or in mouse models lead to similar conclusions that the disease is not due to a loss of the canonical function of these enzymes (Ermanoska et al., 2014; Storkebaum et al., 2009; Stum et al., 2011). On the contrary, recent studies have shown that tRNA synthetase mutations strikingly lead to toxic gains of function, impairing the signaling of different neurotrophic factor receptor families in the nervous system (He et al., 2015; Sleigh et al., 2017; Stum et al., 2011).

Thus, a class of diseases thought to be caused by impaired local translation in compartmentalized signaling is actually caused by the perturbation of another compartmentalized signaling mechanism orchestrated by neurotrophic factors.

Neurons as models for cycling cells

The fundamental mechanisms discussed in this review, although functionally prominent in neurons, are actually shared by most eukaryotic cells, as exemplified in the closing paragraphs of each section above. However, the parallels that exist between these mechanisms in neurons and cycling cells have mostly been appreciated in hindsight, and examples of the use of neurons as models to elucidate new mechanisms of compartmentalized signaling in cycling cells are few and far between. Nonetheless, recent studies into cell length and size sensing have employed precisely this approach, by using sensory neurons as a model to develop and test a hypothesis that was then further validated in fibroblasts, rather than vice versa. Initial modeling in silico suggested that a bidirectional motor-driven mechanism that connected soma with neurite tips could allow neurite length sensing if positive and negative feedback loops were programmed at the respective termini in each direction (Rishal et al., 2012). Experimental validation of this model was achieved first by performing a knockdown screen in sensory neurons (Rishal et al., 2012), and the model's predictions were then validated in both neurons and fibroblasts (Albus et al., 2013; Rishal et al., 2012). Subsequent studies revealed that the underlying mechanism involves anterograde mRNA transport coupled with local translation, and retrograde transport of the de novo synthesized proteins, such that motor-dependent transport and mRNA localization change the balance between protein synthesis in axon versus soma, thereby regulating axon length in sensory neurons (Perry et al., 2016). Again, once the mechanism had been worked out in neurons, it was validated by follow-up experiments in fibroblasts (Perry et al., 2016). Thus, the morphology and size of the neuron pose distinct advantages for the study of compartmentalized signaling, and these advantages can be exploited to obtain new insights that are relevant to a broad spectrum of cell types.

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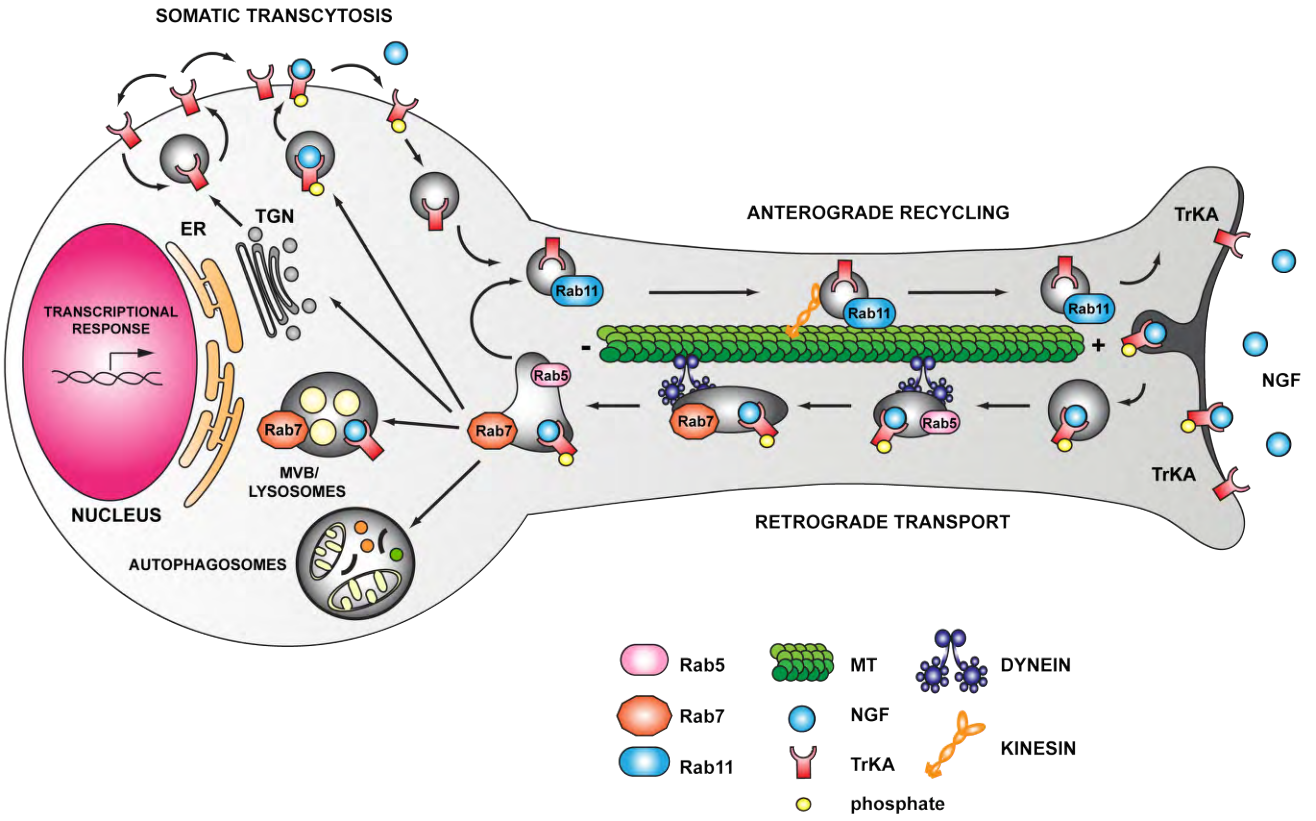
Figure Legends

Figure 1: Trafficking of signaling endosomes. Schematic representation of neurotrophin endosomal trafficking, exemplified by TrkA and NGF. Active TrkA receptor is internalized as a consequence of its binding to NGF. It then undergoes retrograde transport via dynein motor complexes in signaling endosomes (shaded grey) that contain internalized receptors and ligands along microtubules (MT). These endosomes consist of a mixed population of membrane organelles, including multivescicular bodies (MVBs), which are characterized by their association with endocytic markers, such as Rab5 and Rab7. Upon reaching the soma, signaling endosomes are sorted, and the transported receptors enter a variety of pathways, including degradation, recycling to the plasma membrane in Rab11-positive recycling endosomes, transcytosis and the autophagic pathway. Endosomal trafficking of TrkA is instrumental to its correct signaling output.

Figure 2: Axonal local translation mechanisms in injury response and length sensing. This schematic depicts mechanisms of axonal mRNA localization, translation and retrograde transport that underlie injury response and length sensing in neurons. mRNAs undergo anterograde transport by kinesins in axons along microtubules (MT) in complex with their respective RNA-binding proteins (RBP), exemplified in this case as nucleolin and importin β1. Local translation of the cargo RNAs can be induced by injury or at axon tips during active neuronal growth. De novo synthesized proteins, including transcription factors (TF), undergo retrograde transport by dynein via binding to adaptor proteins such as the importins. The dashed line indicates a postulated negative feedback loop, the details of which are still unknown.

Figure 3: Local translation for localized cytoskeletal regulation. This schematic shows the role of local translation in growth cone dynamics. β-actin mRNA undergoes anterograde transport along microtubules (MT) in axons via its interaction with the Zipcode-Binding Protein 1 (ZBP1). mRNA translation occurs in the growth cone as a consequence of a stimulus and is locally regulated in a variety of ways, including through RNA binding protein (RBP) phosphorylation, which causes the RBP to release its cargo mRNA, and through the ubiquitination of the

translated proteins to target them for degradation. The local translation of β-actin mRNA in the growth cone modulates the growth cone's responsiveness to guidance cues and supports axon branching in sensory neurons.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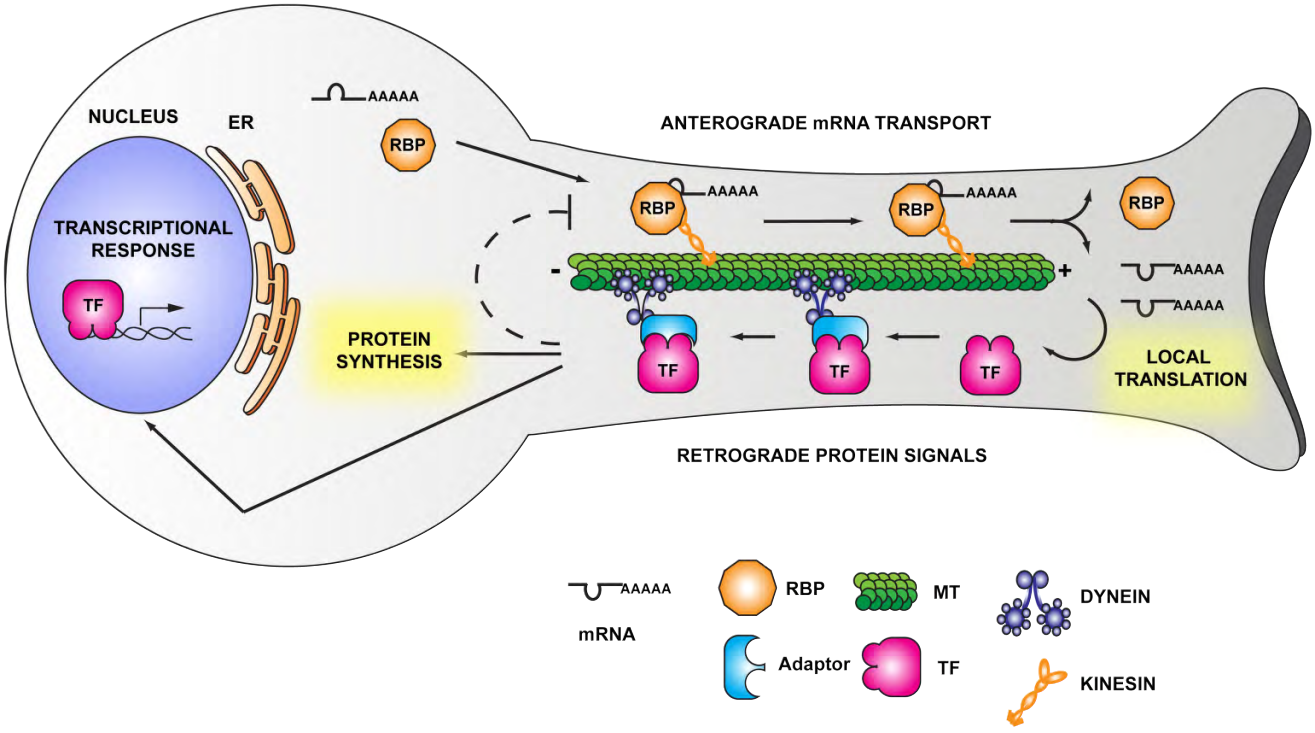
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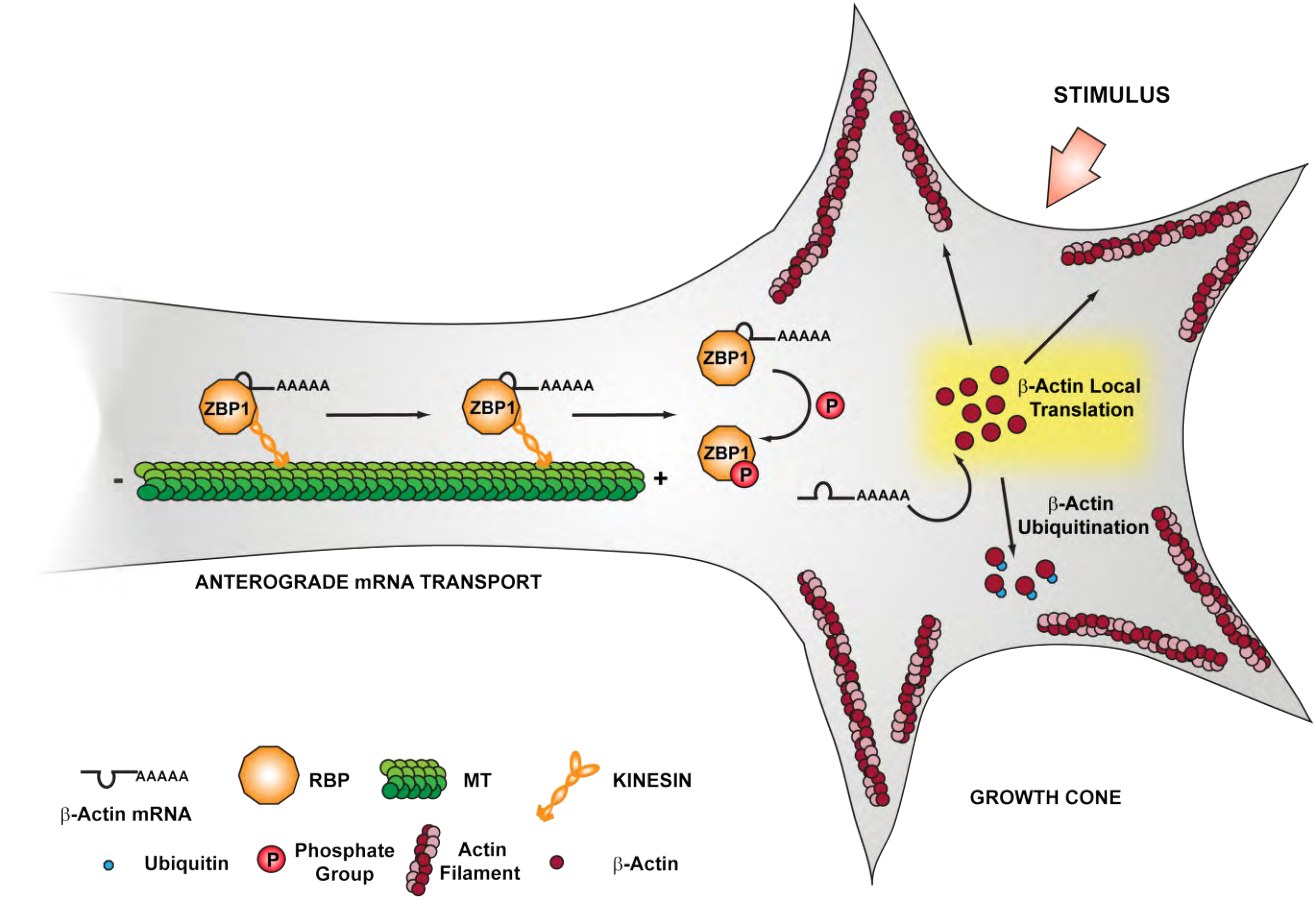
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